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| EXAMINER | |
|---|---|
| JONES, DAMERON LEVEST | |
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/800,531 | ACHILEFU ET AL. | |
| | Examiner | Art Unit | |
| | D L. Jones | 1618 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *1/19/10 & 12/22/09*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *32-35 and 45-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-35 and 54* is/are rejected.

7)☒ Claim(s) *45-53* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**ACKNOWLEDGMENTS**

1. The Examiner acknowledges receipt of the amendment filed 12/22/09. In addition, the Examiner acknowledges receipt of the amendment filed 1/19/10 wherein claims 1-31, 36-44, and 55-57 were canceled and claims 35, 45-51, 53, and 54 were amended.

***Note***: Claims 32-35 and 45-54 are pending.

**RESPONSE TO APPLICANT'S AMENDMENT/ARGUMENTS**

2. The Applicant's arguments and/or amendment filed 12/22/09 and 1/19/10 to the rejection of claims 32-35 and 45-52 made by the Examiner under 35 USC 103, 112, and/or double patenting have been fully considered and deemed persuasive-in-part.

***112 First Paragraph Rejections***

The 112, first paragraph, rejections are WITHDRAWN.

***112 Second Paragraph Rejections***

The 112, second paragraph, rejections are WITHDRAWN.

***Double Patenting Rejection***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated

by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The rejection of claims 32-35 and 54 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 3, 6-9, 11, 14-16, 24, and 26-29 of U.S. Patent No. 6,423,547 is MAINTAINED. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are directed to fluorescent relating methods wherein a cyanine dye is used in combination with a compound such as cyclodextrin. The claims differ in that those of the patented invention do not specifically state that the cyclodextrin is added to enhance the florescence. However, it would have been obvious to one of ordinary skill in the art

that fluorescence is enhanced because a skilled practitioner would recognize that .a composition is inseparable from its properties. Thus, the properties associated with Applicant's product would also be associated with the claims of the instant invention. Hence, both references disclose overlapping subject matter.

***Applicant's Assertion***

In summary, Applicant asserts that the double patenting rejection should be withdrawn because the cited patent does not recite the combining and administering steps. Applicant asserts that when the dye is encapsulated in cyclodextrin, there is a large fluorescence enhancement and that in vivo fluorescence enhancement of dyes co-injected with biocompatible organic solvents has not been previously described. In addition, Applicant asserts that since the claimed outcome of enhanced fluorescence of the composition over the fluorescence of the dye itself is lacking in the claimed outcome of the patent, the rejection should be withdrawn.

***Examiner's Response***

Applicant's arguments are non-persuasive for the following reasons. While the patented invention does not specifically state that the dye is combined with the solvent to result in a composition that is administered to the subject, such steps are not only inherent to the instant method, but supported by the disclosure of the patented invention. Specifically, in column 6, lines 15-23, it is disclosed that the bioconjugates retain the ability to fluoresce for extended periods when compared to the fluorescent dye alone (this would represent 'enhanced' fluorescence). In column 6, Example 1, a dye absent a biocompatible organic solvent is administered to a subject and

*fluorescence is monitored*. In column 7, Example 4, a composition comprising a *solution* of cyclodextrin in water is combined with a dye, indocyanine green. The bioconjugate was analyzed like that of Example 1, administered to a subject and the fluorescence monitored. Patented claims (i.e., claims 14 and 24) involve monitoring fluorescence and claim 24 discloses that the purpose of the method is to increase fluorescent life of the dye. Then, the skilled artisan would recognize that the dye and solvent have been combined and administered to a subject and the fluorescence 'enhanced'. Furthermore, if both Applicant and the patented invention are administering a composition comprising a dye and biocompatible organic solvent/solution, then if a composition is inseparable from its properties, then a skilled practitioner in the art would expect that in both instances the fluorescence would be enhanced.

***103 Rejections***

I. The 103 rejection over Rajagopalan et al (US Patent No. 6,423,547) is WITHDRAWN because of the declaration filed under 37 CFR 1.132 on 12/22/09.

II. The rejection of claims 32-35 under 35 USC 103(a) as being unpatentable over Licha et al (US Patent No. 6,083,485) is MAINTAINED.

III. The rejection of claims 32-35 under 35 U.S.C. 103(a) as being unpatentable over Miwa et al (US Patent No. 7,488,468) is MAITNAINED for the reasons set forth below.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

II. The rejection of claims 32-35 under 35 USC 103(a) as being unpatentable over Licha et al (US Patent No. 6,083,485) is MAINTAINED.

**Licha et al** disclose dyes which may be administered in vivo and radiates in the near infrared radiation region. The fluorescence dyes (e.g., cyanine dyes) may be used for various diagnostic purposes (see the entire document, especially, abstract; column

4, lines 6-28; columns 4-5, bridging paragraph; column 6, lines 17-45; columns 6-7, bridging paragraph). The compounds of Licha et al are water soluble, tolerable, and stable in vitro and in vivo (column 8, lines 31-37). The dye mixture may be administered by intravenous injection and they irradiated with light (column 8, lines 42-49). In addition, Licha et al disclose that for cyanine dyes, increased solubility in water and the presences of hydrophilic groups suppress the formation of aggregates and micelles (column 13, lines 15-22). The dye compositions may optionally contain common adjuvants, diluents, electrolytes, buffers, and substances such as cyclodextrin (column 14, lines 37-52). Thus, it would be obvious to a skilled artisan in the art to combine a cyanine dye with cyclodextrin and administer the compound to a subject because Licha et al disclose that cyclodextrin may be added to the dye. Also, the skilled artisan would recognize that the cyclodextrin is added to the dye prior to being administered to a subject because the prior art discloses that the dye compositions may contain various substances (i.e., such as cyclodextrin) and the compositions may be administered intravenously. In addition, a skilled artisan would be motivated to optimize the biocompatible solvent, cyclodextrin, such that the fluorescence of the mixture when administered to a subject is maximized and aggregation of the dye is minimized.

***Applicant's Assertions***

In summary, Applicant asserts that the skilled artisan would not be motivated to use the compounds/compositions of Licha et al in to enhance fluorescence of any cyanine or indocyanine dyes since the documents have different purposes for using the dyes. In addition, Applicant asserts that Licha et al teaches that their dyes overcome

the prior art problems of toxicity, water solubility, chemical, photophysical, and metabolic stability.

***Examiner's Response***

Applicant's arguments are non-persuasive for the following reasons. First, in the background of Licha et al, the following information is set forth: (1) the main problem with applying near infrared radiation to dyes and detecting the fluorescence (column 1, lines 52-58). In particular, the result is extraordinarily wide scattering of the light which results in a blurred image. (2) In column 2, lines 7-16, it is disclosed that a dye such as indocyanine green has a fluorescent quantum efficiency that is low in a hydrous environment. In addition, it is disclosed that indocyanine green is unstable when dissolved and cannot be applied in saline media because a precipitation will result. Thus, based on the teachings in the background of Licha et al, one would be motivated to use an organic solvent because if a desire to increase the fluorescence quantum efficiency and generate a stable composition once in solution. As a result, the skilled artisan would expect 'enhanced' fluorescence in the organic solvent because the challenges of using non-organic environments are disclosed. (3) A skilled artisan would be able to optimize the dye to solvent amounts for the composition of interest because Licha et al disclose that measurement methods are known to persons skilled in the art and that the expert will know what equipment parameters should be established to obtain optimum recordings and evaluation conditions (column 9, lines 1-6). In column 13, lines 6-23, Licha et al disclose that dyes that are placed in a hydrous environment drop dramatically in fluorescent quantum efficiency values . Thus, leading a skilled

artisan to conclude that an organic environment would yield different results. Furthermore, it is disclosed that the presence of cyclodextrin results in improved stability and solubility (column 14, lines 46-48). Hence, the skilled artisan would recognize that if a substance is present that results in stability of the composition, then according to the background of Licha et al, the environment would more than like be non-hydrous. Also, a skilled artisan would recognize that a composition is inseparable from its properties. As a result, the properties associated with Applicant combining a cyanine dye and cyclodextrin would be the same as that obtain from Licha et al combining their cyanine and cyclodextrin. Thus, while Licha et al disclose that the addition of cyclodextrin is added for a reason different than that of Applicant, the skilled artisan would recognize that the prior art and the instant invention disclose overlapping subject matter since the same components are added to the compositions. Furthermore, in response to Applicant's argument that the use of cyclodextrin, in the instant invention, is to enhance fluorescence, the fact that Applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Hence, the rejection is deemed proper. Therefore, it is the Examiner's position that one of ordinary skill would recognize that both Applicant and the prior art disclose method of 'enhancing' fluorescence.

III. The rejection of claims 32-35 under 35 U.S.C. 103(a) as being unpatentable over Miwa et al (US Patent No. 7,488,468) is MAINTAINED.

**Miwa et al** disclose near infrared fluorescent contrast agents and fluorescence imaging (see entire document, especially, abstract). The contrast agent comprises a cyanine dye (column 2, lines 13-40). The near infrared fluorescent contrast agents of Miwa et al disclose a cyanine dye that is suspended or dissolved in a solvent such as injectable distilled water. Additional additives such as cyclodextrin may be added to adjust osmotic pressure and improve stability and solubility (column 65, lines 7-23). Thus, while Miwa et al does not specifically state that their composition is useful in a method of enhancing fluorescence, it would have been obvious to one of ordinary skill in the art at the time the invention was made to generate a composition comprising a cyanine or indocyanine dye in combination with a cyclodextrin solution useful in a method of enhancing fluorescence for the reasons set forth below. First, both Applicant and the prior art disclose a cyanine dye that may be used in combination with cyclodextrin. Secondly, both the instant invention and that of the prior art are directed to contrast agents that are useful in a method of fluorescence imaging. Third, while the prior art does not specifically state that the purpose of using cyclodextrin (to enhance fluorescence) is the same as Applicant, the fact that Applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). In regards to determining the concentration of cyclodextrin necessary to yield 'enhanced' results, the

quantity of experimentation needed to be performed by one skilled in the art is reasonable (merely routine). A skilled artisan would be motivated to alter the concentration of the carrier solution to obtain maximum results. Thus, both Applicant and the prior art disclose overlapping subject matter.

***Applicant's Assertions***

In summary, Applicant asserts that the teachings of Miwa et al are akin to those of Licha et al and a skilled artisan would not be motivated to alter the carrier solution and obtain maximum results. In addition, Applicant asserts that the purpose of using the dyes of Miwa et al is different from that of the instant invention.

***Examiner's Response***

Applicant's response is non-persuasive for the following reasons. (1) First, just because a document discloses that a substance has superior water solubility does not mean that it is not or cannot be administered in a composition with a biocompatible solvent. For example, Miwa et al specifically discloses that since the fluorescent contrast agent is to be used in a living body, it should be water soluble (column 39, lines 57-59). Applicant's own specification (page 26, lines 11-15) support the teaching of the cited prior art. In particular, Applicant's disclosure set forth that their compositions contain an effective amount of the dye along with conventional pharmaceutical carriers and excipients. As an example of how the parenteral formulations are generated, Applicant discloses that the agents (dyes) may be present in an aqueous (water-containing) solution or suspension. (2) Based on the teachings known in the art regarding the response of dyes when in a completely hydrous environment (see the

background of Licha et al, US Patent No. 6,083,485), the skilled artisan would be motivated to incorporate a biocompatible organic solvent. Thus, for the reasons set forth above disclose in the previous rejection and those set forth in this paragraph, the rejection is deemed proper.

**CLARIFICATION OF THE RECORD**

3. In the response filed 12/22/09 (page 8, lines 16-17), Applicant's comment regarding the elected species of DMSO as the biocompatible organic solvent is noted. The prosecution history is a bit confusing because throughout prosecution, the species cyclodextrin over which prior art has been cited, has bee added and later removed from one or more claims in the amendment (for example, see the amendments submitted 2/26/09; 9/9/09; 10/23/07; 4/9/07; 10/23/07; and 3/15/04). In even the same amendment, the species has been added and deleted. As a result, what the record should reflect is the Examiner's position as noted in the office action mailed 6/10/09 which is as follows: while the entire scope of the claims has not been searched prior art has not been cited for all of the Applicant's organic solvents. Thus, as stated in the action mailed 6/10/09, the specific solvents of claim 51 in combination with the cyanine and indocyanine dyes is not rendered obvious by the prior art. Applicant is once again respectfully requested to amend the independent claims to read on those solvents. The specific solvents that the Examiner is referring to are dimethylsulfoxide, ethyl alcohol, isopropyl alcohol, glycerol, polyol, hydrogenated starch hydrolysate, isomalt, polyglycerol, maltodextrin, starches, polysaccharides, and combinations thereof.

**CLAIM OBJECTIONS**

4. Claims 45-53 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

**COMMENTS/NOTES**

5. The Examiner acknowledges the declaration filed under 37 CFR 1.132 on 12/22/09. The declaration under 37 CFR 1.132 filed 12/22/09 is sufficient to overcome the rejection of claims 32-35 based upon 35 USC 103(a).

6. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D L. Jones whose telephone number is (571)272-0617. The examiner can normally be reached on Mon.-Fri., 6:45 a.m. - 3:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/D L. Jones/
Primary Examiner
Art Unit 1618

March 19, 2010